GEDEON RICHTER LTD.
Established in 1901

European Patent Office
D-80298 München
Germany

Budapest, 11 May 2005
Our ref.: 0302219WOTM

Re: International Search Report and Written Opinion of the International Searching Authority
International application No. PCT/HU2004/000077

Dear Sirs,

We respectfully submit our comments on the Written Opinion as follows:

1. **Reply regarding novelty**

Compounds of formula (I), the solvates of N-hydroxy-valdecoxib, are new compounds.

Document D1 detected non-solvated form of N-hydroxy-valdecoxib, as a metabolite in human urine. A CID-spectrum has been used for the detection. It does not follow from this that the non-solvated N-hydroxy-valdecoxib is a stable substance. The same is true for the glucuronide conjugate of N-hydroxy-valdecoxib, which has been detected by NMR analysis.

There is also a statement in D1 (p 1018) that N-hydroxy-valdecoxib has been synthesized, however, the synthesis has not been described and the substance has not been characterized by macroscopical data and as it is known MS spectra (CID) are not sufficient to support lifetime any substance. Consequently Document D1 does not describe N-hydroxy-valdecoxib thus it can not destroy its novelty.

The basic problem of N-hydroxy-valdecoxib is its decomposing nature to afford easily a sulfinic acid (M7) and a sulfonic acid (M8), which are mentioned as further metabolites in the same document (D1). In this document (D1) there is also two references from the literature (Grzesiok, 1994 and Ruben, 1995) describing this decomposition as a simple non-enzymatic process.

The novelty of the solvates of N-hydroxy-valdecoxib according to the present patent application is the discovery of new and stable derivatives of N-hydroxy-valdecoxib which are all new and stable crystalline substances, characterized by their physicochemical properties as it is written in the application.

It is argued in the Written Opinion that hydrate of N-hydroxy-valdecoxib may presumably be present in human urine in case of a valdecoxib treatment. This is in contradiction with stoichiometric principles. According to the present patent application the solvates are in a 1:1 ratio with N-hydroxy-valdecoxib. In an aqueous solution (eg. in urine) the solvate structures do not exist any more, therefore, compounds of formula (I) can not exist in an aqueous solution.

All of the above mentioned new solvates of N-hydroxy-valdecoxib can be used as active pharmaceutical ingredients, because they are stable enough for storage and formulation.

The novelty of the solvates of N-hydroxy-valdecoxib according to Claims 1 and 2 are therefore well established. For instance a long-term (8 months) standard stability investigation shows that the N-hydroxy-valdecoxib monohydrate is stable.

The non-solvated N-hydroxy-valdecoxib is a glassy substance and decomposes easily releasing NO to give sulfinic and sulfonic acids. Therefore, although the novelty could not be destroyed by prior art as mentioned above, we agree that the non-solvated N-hydroxy-valdecoxib should be cancelled from the claimed compounds.

2. Reply regarding inventive step

Document D2 described an active metabolite of valdecoxib, which is C-hydroxylated derivative of valdecoxib. Its synthesis has been described in the document D2 and also its pharmacological activity has been summarized. This metabolite was less potent than valdecoxib in the adjuvant arthritis assays.

On the other hand N-hydroxy-valdecoxib monohydrate according to the present patent application proved to be more potent than valdecoxib in two in vivo animal tests: 1.) in monoarthritis model in rats (incapacitance test) and 2.) in the chronic model of Randall-Selitto test. It is also interesting that N-hydroxy-valdecoxib monohydrate improved the coronary blood flow in rabbit heart in a Langendorff-type perfusion test. A study performed on the effects of valdecoxib and a compound of present application on neurochemical transmission of the isolated main pulmonary artery of the rabbit shows that Compound of formula (I) significantly inhibited the stimulation-evoked contractions of rabbit pulmonary artery smooth muscle cells. This effect (vasodilatation) may have therapeutic significance, since the "coxib"-family slightly increases the blood pressure in humans, which is probably responsible for their side effects. This observation has a special importance because of the known cardiac side-effects of the known coxibs and also in case of valdecoxib.

In agreement with the statement of the Written Opinion it is logical to investigate the metabolites, but it was unexpectable that a minor submetabolite could be more potent than the original drug. This was one of the serendipities of the present patent application.

Based of the above arguments Claims 1-5 and Claims 14-21 have a clear and unquestionable inventive step.

As for the process Claims 8-11, we would like to draw the attention to the document D4 (p 2098). This journal article shows, how unstable these N-hydroxysulfonamides can be. In case of 4-nitrobenzenesulfonhydroxamide the following text is written int the journal article: „The compound was so unstable that the melting point had to be determined immediately after crystallisation and drying and even then there was evidence of decomposition". Document D3 is not relevant, because it has an essential different structure as a saccharin derivative, where the N-hydroxy-sulfonamide is „double" acylated and it is not comparable to the compounds of the present patent application.

It is a remarkable and unexpected achievement of the present patent application that the product stability could be obtained not only by the solvate forms, but it was also supported by using ascorbic acid during the crystallisation.

Regarding Claims 12 and 13 it is to be noted that the withdrawal of the non-solvated N-hydroxy-valdecoxib from the claimed compounds supersedes these claims.

3. Other remark

In case of Claim 8 we described two alternatives to prepare the N-hydroxysulfonamides. There is a missing „or" between a.) and b.) processes.

In compliance with the above we submit a new set of claims to the WIPO and to you.

Enclosure
New set of claims

Yours sincerely,

Dr. István Polgár
Director, Intellectual Property